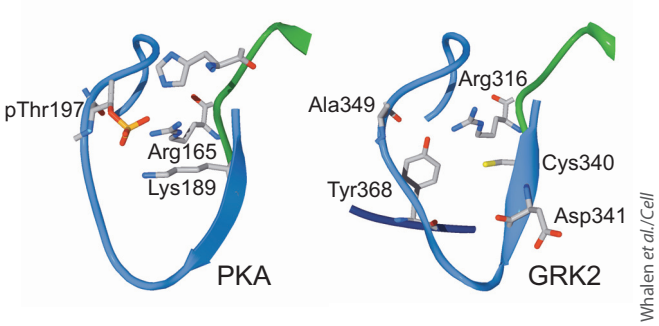
Kidney International (2007) **72**, 245–246. doi:10.1038/sj.ki.5002431

Regulation of G protein-coupled receptor signaling by nitric oxide

G protein-coupled receptors (GPCRs) constitute the largest known family of cell-surface receptors and are fundamentally involved in mammalian physiology. β-adrenergic receptors (β-ARs) and AT_1 angiotensin receptors are prototypical GPCRs, both playing a critical role in the regulation of cardiovascular, pulmonary, renal, and other functions. Ligand signaling by GPCRs is quickly followed by receptor desensitization. But, in addition, loss of receptor responsiveness may contribute to disease. For example, loss of β-AR responsivity is thought to be linked to both heart failure and asthma. The GPCR kinases (GRKs) curtail G protein signaling by phosphorylating agonist-occupied receptors and promoting their desensitization, internalization, and downregulation.



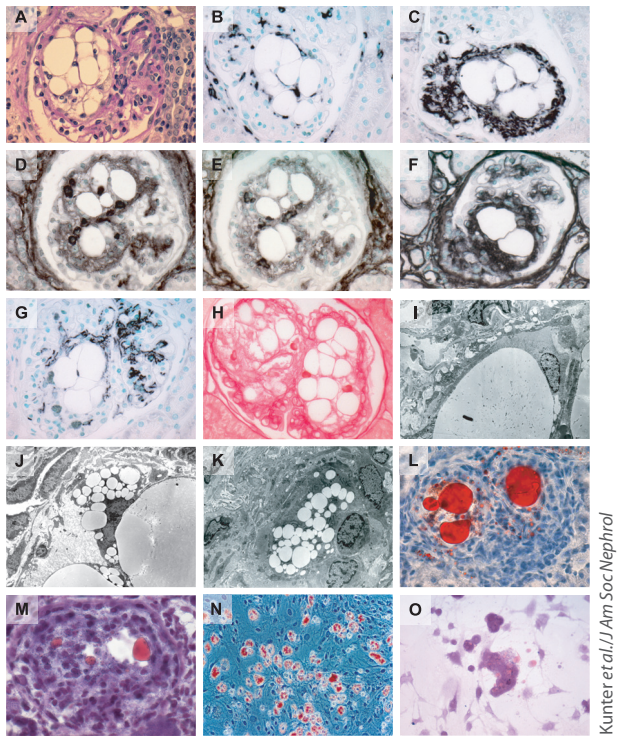
Activation loops of GRK2 and cyclic AMP-dependent protein kinase (PKA), a prototypic AGC kinase.

Nitric oxide (NO) and low-molecular weight *S*-nitrosothiols (SNOs) regulate a diverse array of signal transduction pathways, acting in significant part through the covalent modification (*S*-nitrosylation) of cysteine residues that are found at active or allosteric sites of proteins. Recent evidence indicates that signaling through GPCRs might also be regulated by *S*-nitrosylation. For example, exposure of cells and tissues to nitrosylating agents inhibits or potentiates the signaling of multiple GPCRs, and the cysteine residues that confer NO responsivity have been identified in the β_2-AR and AT_1 angiotensin receptors. Interestingly, diminished responsiveness to β_2-AR agonists as assessed by vasodilation can be reversed by administration of SNOs, and mice with a genetic alteration that impairs breakdown of SNOs are protected from tachyphylaxis. In a recent communication, Whalen *et al.* investigated the molecular mechanism(s) by which NO or SNOs preserve β-AR function. They found in mice that SNOs increased β-AR expression and prevented agonist-stimulated receptor downregulation. In cells, SNOs decreased GRK2-mediated β-AR phosphorylation and subsequent recruitment of β-arrestin to the receptor, resulting in attenuation of receptor desensitization and internalization. In both cells and tissues, GRK2 (Figure) was *S*-nitrosylated by SNOs as well as by NO synthases, and GRK2 *S*-nitrosylation increased after stimulation of multiple GPCRs with agonists. The Cys340 of GRK2 was identified as a principal locus of inhibition by *S*-nitrosylation. These elegant studies reveal a central molecular mechanism through which GPCR signaling is regulated. (*Cell* 2007; **129**: 511–522)

Juan Oliver

Mesenchymal stem cells prevent renal failure but maldifferentiate into glomerular adipocytes

Glomerulonephritis is a major cause of renal failure. In a new study, Kunter *et al.* sought to determine whether intrarenal injection of rat mesenchymal stem cells (MSCs) can preserve renal function. At day 10, fluorescently labeled rat MSCs localized to more than 70% of glomeruli, ameliorated acute renal failure, and reduced glomerular adhesions. Fifty days later, proteinuria had progressed to 40 ± 25 mg per day in controls but stayed low in MSC-treated rats (13 ± 4 mg per day; $P < 0.01$). At day 60, renal function was better in the MSC group than in medium controls. Kidneys of the MSC group on day 60 contained 11% more glomeruli per 1 mm^2 section of cortex but also significantly more collagen types I, III, and



Morphology of adipocytes in MSC-treated Lewis rats with anti-Thy1.1 nephritis on day 60.

IV and α-smooth muscle actin as compared with controls (Figure). Approximately 20% of the glomeruli of MSC-treated rats contained single, or clusters of, large adipocytes with pronounced surrounding fibrosis. Adipocytes exhibited fluorescence in their cytoplasm and/or intracellular lipid droplets. Lipid composition in these adipocytes *in vivo* mirrored that of MSCs that underwent adipogenic differentiation *in vitro*. The early beneficial effect of MSCs of preserving damaged glomeruli and maintaining renal function was offset by a long-term partial maldifferentiation of intraglomerular MSCs into adipocytes, accompanied by glomerular sclerosis. These data suggest that MSC treatment can be a valuable therapeutic approach only if adipogenic maldifferentiation is prevented. (*J Am Soc Nephrol* 2007; **18**: 1754–1764)

Marc De Broe

Diagnostic thresholds for ambulatory blood pressure

Blood pressure measurement is the basis for the diagnosis and treatment of hypertension. Conventional blood pressure measurement by auscultation of the Korotkoff sounds is fraught with potential sources of error. Ambulatory monitoring allows registration of the blood pressure throughout the entire day in subjects engaged in their usual activities. Ambulatory blood pressure recordings have high reproducibility, are not subject to digit preference, and avoid the transient rise of a patient's blood pressure in response to a medical environment, the so-called white-coat effect.

Although blood pressure is continuously distributed, clinicians need a diagnostic frame of reference to interpret ambulatory blood pressure values and to classify patients. Current guidelines propose operational thresholds for the ambulatory blood pressure, but these limits are not outcome driven, relying largely on the distribution of the ambulatory blood pressure in normotensive reference populations or on the regression of ambulatory on conventional blood pressure. Kikuya *et al.* thus constructed an international population-based database with the objective of determining diagnostic thresholds for ambulatory blood pressure monitoring in terms of cardiovascular outcome.

They performed 24-hour ambulatory blood pressure monitoring in 5682 participants (mean age 59.0 years; 43.3% women) enrolled in several prospective population studies. In multivariate analyses, they determined pressure thresholds, which yielded 10-year cardiovascular risks similar to those associated with optimal (120/80 mm Hg), normal (130/85 mm Hg), and high (140/90 mm Hg) blood pressure on office measurement. During 9.7 years (median), 814 cardiovascular events occurred, including 377 strokes and 435 cardiac events. Rounded thresholds for optimal ambulatory blood pressure amounted to 115/75 mm Hg for 24 hours, 120/80 mm Hg for daytime, and 100/65 mm Hg for nighttime. Rounded thresholds for normal ambulatory blood pressure were 125/75, 130/85, and 110/70 mm Hg, respectively, and those for ambulatory hypertension were 130/80, 140/85, and 120/70 mm Hg. These data, obtained from a large international database from a random sample of the general population, are of great interest and give calculated thresholds generally lower than previously estimated. A randomized therapeutic trial is now needed to test whether ambulatory blood pressure is superior to traditional blood pressure measurements used in the clinic. (*Circulation* 2007; **115**: 2145–2152)

Juan Oliver

Acute and chronic complications of type 2 diabetes mellitus in children and adolescents

With the increase in prevalence of type 2 diabetes mellitus in adolescents, clinicians anticipate a rise in incidence of secondary comorbidities, including hypertension, hyperlipidemia, nephropathy, and retinopathy. Findings of studies in young adults have suggested that the development and progression of clinical complications might be especially rapid when type 2 diabetes develops early in life, raising the possibility of a serious public-health challenge in the next few decades. Furthermore, adolescents with type 2 diabetes show poor adherence to medical care and treatment and, therefore, could be at especially high risk for development of early complications. To date, reports of the epidemiology and natural history of secondary complications specifically in adolescents with type 2 diabetes have been scarce. A new review by Pinhas-Hamiel and Zeitler shows evidence of more aggressive development of clinical complications — particularly microalbuminuria and risk of myocardial infarction — in adults diagnosed with type 2 diabetes between the ages of 18 and 44 years than in those identified after 45 years of age. Their detailed analysis of the literature found evidence of acute complications, including diabetic ketoacidosis, hyperglycemic hyperosmolar state, and malignant hyperthermia-like syndrome with rhabdomyolysis. Chronic complications identified in their analysis included hypertension, microalbuminuria, background retinopathy, dyslipidemia, non-alcoholic fatty liver disease, cardiovascular and atherosclerotic complications, neuropathy, psychiatric disorders, health-related quality of life, and gestational diabetes.

The authors conclude that changes to substantial morbidity and mortality have been reported in children and adolescents with type 2 diabetes. They highlight that microvascular complications can be present at the time of diagnosis and have a higher rate of progression in young people with type 2 diabetes than in those with type 1 diabetes. These findings, although still limited, suggest the urgent need to develop awareness and early management of type 2 diabetes and associated abnormalities. In addition, long-term studies are needed to establish the value of early initiation of adjunctive treatments. (*Lancet* 2007; **369**: 1823–1831)

Marc De Broe